REMARKS

I. Status of the Claims

Claims 18-34 are pending, with claim 31 having been withdrawn from consideration by the Examiner. Claims 26 and 32 have been amended by this Response, as discussed further below, and their amendment presents no new matter issue.

II. Restriction Requirement

Applicants note the finality of the restriction requirement and confirm the election of Group I, claims 18-25 and 31, as set forth in Applicants' Amendment and Response filed March 11, 2002, pg. 16.

III. Information Disclosure Statement

The Examiner contends that the Information Disclosure Statement (IDS) filed on June 5, 2002, failed to comply with 37 C.F.R. § 1.98(a)(2) because no copies of the referenced applications were provided. (Office Action, pg. 7.) This is incorrect. Applicants' filing and the U.S. Patent and Trademark Office receipt of the copies of cited applications are evidenced by the enclosed date-stamped postcard, which lists, as item 2, "PTO Form 1449 w/*listed documents attached*" (emphasis added) and which bears the U.S. Patent and Trademark Office OIPE date of receipt stamp of June 5, 2002. M.P.E.P. § 503.[1] Accordingly, Applicants fully complied with Section 1.98(a)(2), and no further action should be required before the Examiner fully considers Applicants' June 5, 2002, IDS. *See* 37 C.F.R. § 1.98(d).

[1] "A postcard receipt which itemizes and properly identifies the papers which are being filed serves as prima facie evidence of receipt in the PTO of all items listed thereon on the date stamped thereon by the PTO." M.P.E.P. § 503.

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However, in view of the fact that two of the three applications cited in the June 5, 2002, IDS have now issued as patents, Applicants present herewith a new IDS under 37 C.F.R. § 1.97(c)(2). The new IDS identifies the two patents (U.S. Patent Nos. 6,541,451 B1 and 6,569,854 B1) as well as the third application (U.S. Application No. 10/055,888) from the June 5, 2002, IDS. Copies of the two patents and the third application are also provided. Applicants request that the Examiner consider these references and acknowledge that they were considered by initialing the PTO 1449 filed herewith.

IV. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 18-30 and 32-34 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter allegedly not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. (Office Action, pg. 3-5.) Applicants respectfully traverse the rejection.

The Examiner contends that there is no evidence that the claimed compounds are effective to inhibit growth of bacteria. (Office Action, pg. 3.) The Examiner further contends that structure/activity relationships of antibacterial compounds are unpredictable, undue experimentation would be required to determine which of the claimed compounds will inhibit bacterial growth, and even if the compounds exhibited antibacterial activity *in vitro*, undue experimentation would be required to determine which of the claimed compounds can be used to treat even one disease caused by bacteria. (Office Action, pg. 5.) Applicants respectfully disagree with each of these contentions.

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1. **Evidence of Antibacterial Activity**

The argument that there is no evidence in the record of activity is simply incorrect. First, as explained on page 7, line 21 to page 8, line 10 of the specification, compounds of formula (I) are potent by both the oral and parenteral routes. Second, *in vitro*, in combination with pristinamycin II_B, compounds of general formula (I) have proven active at concentrations of between 0.25 and 16 mg/l on Staphylococcus aureus 209P. (Specification, pg. 33, ln. 1-4.) Third, *in vivo*, on experimental infections of mice with Staphylococcus aureus IP 8203, compounds of general formula (I) have proven active at doses of between 15 and 150 mg/kg, combined with pristinamycin II_B, and between 5 and 150 mg/kg subcutanesouly, combined with dalfopristin (CD_{50}) in 30/70 combinations. (Specification, pg. 33, ln. 5-11.) Accordingly, there is evidence of record that the claimed compounds have antibacterial activity.

The Examiner's citation of references disclosing pyridazine N-oxides, haliangicin, cecropin-melittin hybrid peptides, and amphipathic antimicrobial peptides that are apparently inactive as anti-bacterials (Office Action pg. 3-4), does not provide an appropriate basis for discounting the unambiguous evidence of activity found in the present specification. This view is supported by the Federal Circuit, which has held that:

> a specification disclosure which contains a teaching of the manner and processes of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of Section 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support.

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In re Brana, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (citations and quotations omitted) (emphasis in the original). Therefore, even if some *other* classes of compounds, i.e., other than the claimed compounds, include inactive species, there is "no reason to doubt the objective truth of the statements" in the present specification regarding (1) activity via oral and parenteral routes, (2) *in vitro* activity, and (3) *in vivo* activity of the claimed compounds. The Examiner's citation to other classes of compounds also fails to call into question the fact that streptogramin compounds are known antibacterials (see, for example, J.C. Barrière et al, "Recent developments in streptogramin research," Current Pharmaceutical Design, (4), 155-180 (1998) ("[t]he streptogramins are a class of antibiotics remarkable for their antibacterial activity and unique mechanism of action." (Abstract)), copy enclosed for the Examiner's convenience), or that the specification makes a credible showing that the claimed compounds are also active.

2. <u>No Undue Experimentation Would be Required</u>

Even if there are compounds within the scope of general formula (I) that are not active anti-bacterials (though the Examiner has cited no evidence of this), claims may contain inoperative embodiments and still meet the enablement requirements of Section 112. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984). Although courts have held invalid claims covering inoperative embodiments where there was no adequate disclosure to teach one skilled in the art how to determine operative from inoperative embodiments without undue experimentation, *e.g., In re Sichert* 196 USPQ 209 (CCPA 1977), the present situation is distinct.

In particular, one skilled in the art *would* know how to distinguish operative from inoperative embodiments. For example, the Examiner's citation of several references

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related to the testing of other classes of antibacterial agents (Office Action, pg. 3-4), where inactive compounds were identified and separated from active compounds, unambiguously demonstrates that the determination of antibacterial activity is within the skill of the art. Accordingly, even if general formula (I) includes compounds that are not active antibacterials, the claims are enabled since, as in *Atlas*, one skilled in the art could readily distinguish operative from inoperative embodiments.

Therefore, in view of, for example, the apparent skill in the art demonstrated by the Examiner's references, where active compounds are readily distinguished from inactive compounds, the present claims meet the requirements of Section 112. *See, e.g., In re Cook*, 169 USPQ 298, 302 (CCPA 1971). That is, since the determination of antibacterial activity is routine and within the skill of the art, *undue* experimentation is not required to determine which of the claimed compounds will inhibit bacterial growth. *See Johns Hopkins Univ. v. CellPro, Inc.* 47 USPQ2d 1705 (Fed. Cir. 1998) (holding claims enabled even if routine experimentation is required).

Furthermore, with respect to the Examiner's contention that undue experimentation would be required to determine which of the claimed compounds can be used to treat even one disease caused by bacteria (Office Action, page 5), an inappropriate standard for enablement has been applied. For example, claims directed to "treatment of diseases" and "antitumor substances" were found to be enabled by a statement that the claimed compounds had "a better action and better action spectrum as antitumor substances" as compared to certain known compounds. *In re Brana*, 24 USPQ 1436, 1440 (Fed.Cir. 1995). Also, routine experimentation *is* allowed. *Johns Hopkins Univ. v. CellPro, Inc.* 47 USPQ2d 1705 (Fed. Cir. 1998).

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The evidence in the present specification that compounds of general formula (I) have *in vivo* activity on experimental infections of mice with Staphylococcus aureus IP 8203 (Specification, pg. 33, ln 5-11), is even more substantial than the support found to enable the claims in *Brana*. Further, Applicants need not demonstrate that any of the compounds will be ultimately useful in humans because "one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans." *Brana* at 1442 (quoting *In re Krimmel*, 130 USPQ 215, 219 (CCPA 1961). The Federal Circuit has made an express policy decision not to require human testing of pharmaceuticals to show enablement because "the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas...." *Id.*

3. Conclusion Regarding Rejections Under 35 U.S.C. § 112, First Paragraph

For at least the reasons that (1) there is clear evidence of activity and enablement in the specification, (2) the citation of inactivity in other antibacterial categories is less specific, and therefore less relevant, than the evidence of record, and (3) non-operative embodiments (to the extent they exist) are not a bar to patentability where, as here, it is merely routine skill to identify active from inactive compounds, the rejection is in error. Reconsideration and withdrawal are respectfully requested.

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V. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 26-30 and 32-33 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The specific rejections are addressed in turn.

1. Claim 26

The Examiner contends that claims 26-30 are indefinite for "failure to recite a step for isolating the final production." (Office Action, pg. 6 (emphasis added).) The Examiner further contends that "[i]f a chemist abstains from isolating the target compound from this [reaction product] mixture, then he is not in possession of the final product. To equate a mixture with a pure compound is simply an invalid proposition" (*Id.*) Applicants respectfully disagree with and traverse the rejection.

Claim 26 is directed to "[a] process for preparing a group B streptogramin derivative ...." The Examiner agrees that "[a]t the end of the reaction processes, one will be left with ... [, among other things,] the target compound ...." (*Id.*) Thus, there should be nothing indefinite about the claims.

Neither the preamble nor any element of claim 26 requires that a group B streptogramin derivative be prepared in a pure form or that it be isolated. The possibility that the claims read on processes where a group B streptogramin derivative is not isolated in pure form is of no moment. Further, claim 26 uses the open structure of "comprising," thereby allowing for the formation of other materials as well as a group B streptogramin derivative.

Accordingly, since the Examiner agrees that the claimed process will result in the target compound (a group B streptogramin derivative) (Office Action, pg. 6), there is nothing indefinite in the claim, regardless of whether an isolation step is expressly

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included or not. Reconsideration and withdrawal of this rejection are respectfully requested.

The Examiner further contends that Claim 26 is indefinite for encompassing processes in which the time and conditions are not effective to form a compound according to formula (I). (Office Action, pg. 7.) Applicants respectfully disagree with and traverse the rejection. However, in order to advance prosecution, part (a) of claim 26 to has been amended herein to read "reacting, for a time and under conditions sufficient to form the group B streptogramin derivative, an enaminoester of formula (II):" Accordingly, the rejection is moot.

2. Claim 32

Claim 32 was rejected for characterizing diluents and adjuvants as "agents," a term the Examiner contends is normally associated with active ingredients. (Office Action, pg. 6.) Applicants respectfully disagree with and traverse the rejection. Nevertheless, in order to advance prosecution, the term "agent" in claim 32 has been replaced with the term --component--. Accordingly, the rejection is moot.

Claim 32 was also rejected for the use of "optional" components such that the claim reads on a single component (a group B streptogramin) when no optional component is present. (Office Action, pg. 6.) Claim 32 has been amended herein to moot this rejection.

Reconsideration and withdrawal of the rejection are respectfully requested.

3. Claim 33

Claim 33 was rejected, apparently for its reference to Streptogramin A derivatives by their common name, such as pristinamycin II_B, and not their chemical name or

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structure. (Office Action, pg. 7 ("Claim 33 makes reference to various group A streptogramin derivatives such as pristinamycin II_B. However, this renders the claim indefinite. It is suggested that a chemical name or structure be provided for each of the listed compounds.") Applicants respectfully traverse the rejection.

There is nothing improper in using terms, such as common names for compounds, if they are well known and understood in the art. *E.g., In re Miller*, 164 USPQ 597, 599 (CCPA 1971). In the present case, the common names, such as pristinamycin II_B, which are used are well known in the art. *See, e.g.,* J.C. Barrière et al. at 156 (copy enclosed). Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

VI. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

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Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: Monday, June 23, 2003

By: _____

Mark J. Feldstein
Reg. No. 46,693

Enclosure:

- J.C. Barrière et al, "Recent developments in streptogramin research," Current Pharmaceutical Design, (4), 155-180 (1998).
- Copy of June 5, 2002, date stamped postcard evidencing receipt by U.S. Patent and Trademark Office of PTO-1449 and listed documents.

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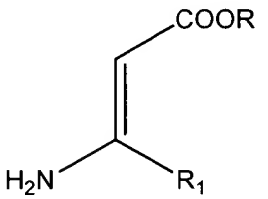
APPENDIX TO AMENDMENT OF JUNE 23, 2003

Version with Markings to Show Changes Made

Amendments to the Claims

26. (Amended) A process for preparing a group B streptogramin derivative according to claim 18, wherein said Y is chosen from said $=CR_3-$ groups, and said R_3 is not an alkyl group, said process comprising:

(a) reacting, for a time and under conditions sufficient to form the group B streptogramin derivative, an enamino ester of formula (II):



(II)

wherein R_1 is chosen from R_1 of formula (I) and R is chosen from alkyl groups and residues of easily hydrolysable esters, wherein said residues are other than said alkyl groups,

with a 5 -methylenepristinamycin derivative of formula (III):

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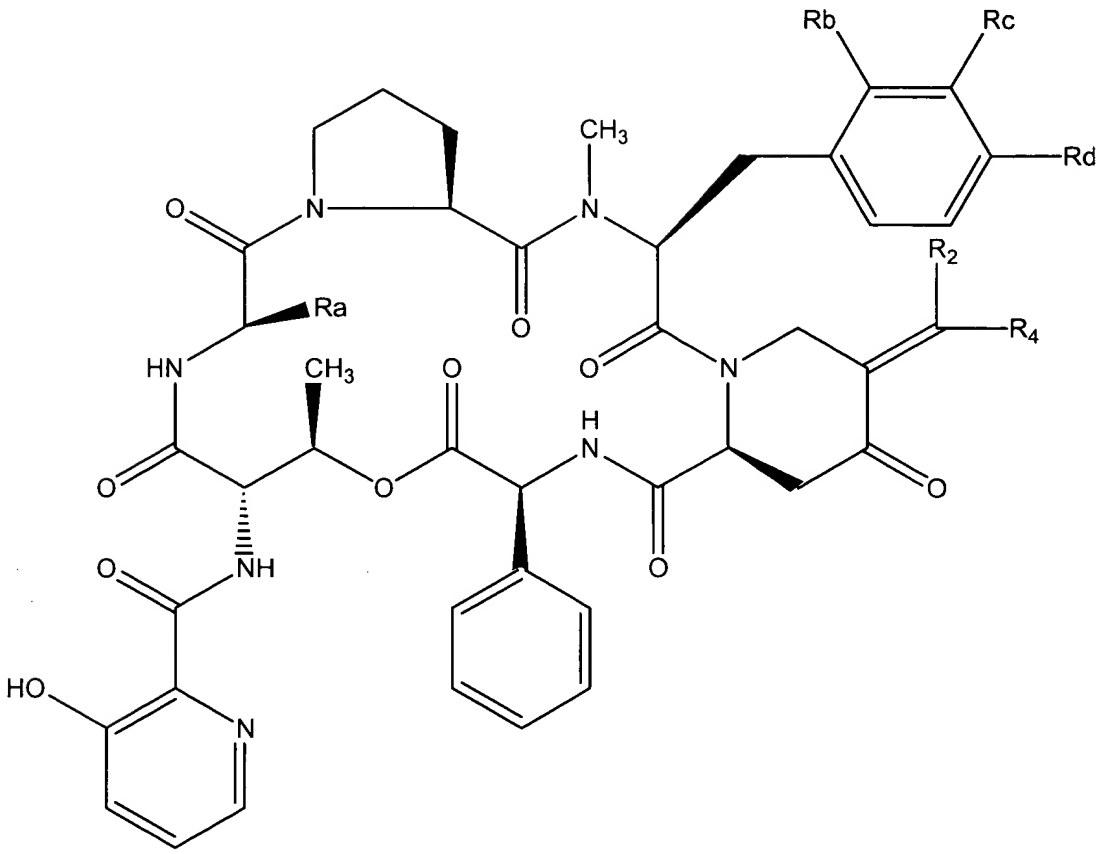

(III)

wherein

- Ra, Rb, Rc, and Rd are chosen from, respectively, Ra, Rb, Rc, and Rd of formula (I),

(i) - R_2 is chosen from R_2 of formula (I), and

- R_4 is a hydrogen atom, or

(ii) - R_2 is a hydrogen atom, and

- R4 is chosen from a hydrogen atom and dialkylamino groups,

(b) optionally, where appropriate, converting said group B streptogramin derivative, prepared by (a) above, to a group B streptogramin derivative, wherein said R_3 is a carboxyl group,

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(c) optionally decarboxylating said group B streptogramin derivative, prepared by (b) above, wherein said R_3 is a carboxyl group, to a group B streptogramin derivative, wherein said R_3 is a hydrogen atom, or

(d) optionally converting said group B streptogramin derivative, prepared by (b) above, wherein said R_3 is a carboxyl group, to a group B streptogramin derivative, wherein said R_3 is a carbamoyl group,

(e) optionally converting said group B streptogramin derivative, prepared by (a) or (c) above, wherein said R_1 is a hydroxymethyl group, to a group B streptogramin derivative, wherein said R_1 is a formyl group, and

(i) optionally converting said group B streptogramin derivative, wherein said R_1 is a formyl group, to a group B streptogramin derivative, wherein said R_1 is a carboxyl group, and

(ii) optionally converting said group B streptogramin derivative, wherein said R_1 is a carboxyl group, to a group B streptogramin derivative, wherein said R_1 is chosen from alkyloxycarbonyl groups and –CONR'R" groups, and

(f) optionally mono-N-demethylating said group B streptogramin derivative, prepared by (a), (b), (c), (d), or (e) above, wherein Rd is a dimethylamino group, to a group B streptogramin derivative, wherein Rd is a methylamino group, and

(g) optionally converting said group B streptogramin derivative, prepared by (a), (b), (c), (d), (e), or (f) above, to a salt.

32. (Amended) A pharmaceutical composition comprising at least one group B streptogramin derivative or salt thereof according to claim 18, wherein said

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composition further comprises at least one component chosen from (i) ~~optionally comprises~~ at least one compound chosen from group A streptogramin derivatives and salts thereof, and (ii) ~~optionally comprising~~ at least one ~~agent~~ component chosen from pharmaceutically acceptable diluents and pharmaceutically acceptable adjuvants.

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PLEASE STAMP TO ACKNOWLEDGE RECEIPT OF THE FOLLOWING:

In Re Application of: Pascal **DESMAZEAU et al.**

Application No.: 09/643,197 Group Art Unit: 1653

Filed: August 22, 2000 Examiner: D. Lukton

For: STREPTOGRAMIN DERIVATIVES, PREPARATION METHOD AND COMPOSITIONS CONTAINING SAME

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1. Information Disclosure Statement Under 37 C.F.R. § 1.97(b)
2. PTO Form 1449 w/listed documents attached
3. Amendment and Response to Modified Restriction Requirement
4. Change of Correspondence Address
5. Petition for Extension of Time (one (1) month)
6. Check in the amount of $110.00

Dated: June 5, 2002 (Due Date: June 8, 2002)

Docket No.: 3806.0497-00

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